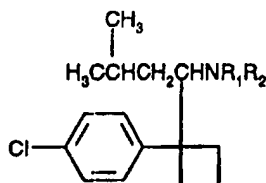


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(54) Title: **USE OF SIBUTRAMINE ANALOGUES TO LOWER LIPID LEVELS**

(I)

(57) Abstract

A compound of formula (I) or a pharmaceutically acceptable salt thereof in which R₁ and R₂ are independently H or methyl (for example *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl amine hydrochloride optionally in the form of its monohydrate) is used for lowering lipid levels and/or increasing the HDL : LDL cholesterol ratio in humans, for example in humans having hyperlipidaemia, hypercholesterolaemia or hypertriglyceridaemia.

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USE OF SIBUTRAMINE ANALOGUES TO LOWER LIPID LEVELS

This invention relates to a method of improving lipid levels in the human body.

5 Complications of atherosclerosis, such as myocardial infarction, stroke and peripheral vascular disease are a major cause of mortality and morbidity. In addition, the quality of life of millions of people is adversely affected by angina and heart failure caused by coronary heart disease. Hyperlipidaemia has been associated with an increased risk of developing these conditions. For this reason it is desirable to
10 understand the etiology of hyperlipidaemia and to develop effective treatments for this condition. Hyperlipidaemia has been defined as plasma cholesterol and triglyceride levels that exceed "normal" (95th percentile of levels of the general population) levels. However, the ideal cholesterol level is much less than the normal level of the general population. Many people have cholesterol levels above the ideal
15 (hypercholesterolaemia) and are therefore at an elevated risk of coronary artery disease (CAD). It is known that reducing the cholesterol level in such people is very effective in reducing the risk of CAD. Hypertriglyceridaemia may also be involved in atherosclerosis and can, in extreme cases, cause potentially life-threatening pancreatitis.

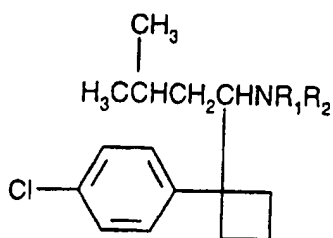
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 There are several ways in which treatment of people with high lipid levels can be beneficial. These include lowering the total cholesterol level, lowering the total triglyceride level and increasing the ratio of high density lipoprotein (HDL) cholesterol to low density lipoprotein (LDL) cholesterol. This latter improvement is important
25 because there is evidence that LDL is proatherogenic and HDL is antiatherogenic so that increasing HDL : LDL ratio provides a degree of protection from atherosclerosis and CAD.

 Hyperlipidaemia can arise through a genetic disorder, as a result of other
30 medical conditions or environmental influences, or a combination of these factors. Surprisingly, it has now been found that the administration of certain arylcyclobutylalkylamine compounds is effective in reducing lipid levels, particularly cholesterol and triglyceride levels.

35 Accordingly, the present invention provides a method for the prophylaxis and/or treatment of hyperlipidaemia, hypercholesterolaemia or hypertriglyceridaemia,

comprising the administration, to a human in need thereof, of a therapeutically effective amount of a compound of formula I



including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl, in conjunction with a pharmaceutically acceptable diluent or carrier.

The method may also be used for the prophylaxis of atherosclerosis, coronary heart disease and/or coronary artery disease in humans at increased risk of developing these conditions.

The preparation and use of compounds of formula I, such as *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine (or *N*-{1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutyl}-*N,N*-dimethylamine) and salts thereof, in the treatment of depression is described in British Patent Specification 2098602. The use of compounds of formula I such as *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and salts thereof in the treatment of Parkinson's disease is described in European Patent Number 282206. The use of *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and salts thereof in the treatment of cerebral function disorders is described in US Patent 4939175. The use of *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride in the treatment of obesity is described in European Patent Number 397831. A particularly preferred form of this compound is *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate (sibutramine hydrochloride monohydrate) which is described in European Patent Number 230742. The use of *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and salts thereof for improving the glucose tolerance of humans having Impaired Glucose Tolerance or Non-Insulin Dependent Diabetes Mellitus is described in published PCT application WO95/20949.

It may be appreciated by those skilled in the art that compounds of formula I may exist as salts with pharmaceutically acceptable acids. Examples of such salts

include hydrochlorides, hydrobromides, sulphates, methanesulphonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid. Compounds of formula I and their salts may exist
5 in the form of solvates (for example hydrates).

It will be appreciated by those skilled in the art that compounds of formula I contain a chiral centre. When a compound of formula I contains a single chiral centre it may exist in two enantiomeric forms. The present invention includes the use of the
10 individual enantiomers and mixtures of the enantiomers. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallisation; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective reaction
15 of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer
20 is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

25

Specific compounds of formula I are *N,N*-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine, *N*-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-*N*-methylamine, and 1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine including racemates, individual enantiomers and mixtures thereof, and pharmaceutically
30 acceptable salts thereof. A preferred compound of formula I is *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine or a salt thereof, for example the hydrochloride salt. A preferred form of this hydrochloride is its monohydrate.

The compound of formula I may be administered in any of the known
35 pharmaceutical dosage forms. The amount of the compound to be administered will depend on a number of factors including the age of the patient, the severity of the

condition and the past medical history of the patient and always lies within the sound discretion of the administering physician but it is generally envisaged that the dosage of the compound to be administered will be in the range 0.1 to 50 mg preferably 1 to 30 mg per day given in one or more doses.

5

Oral dosage forms are the preferred compositions for use in the present invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared from a mixture of the active compound with fillers, for example calcium phosphate; disintegrating agents, for example maize starch; lubricating agents, for example magnesium stearate; binders, for example microcrystalline cellulose or polyvinylpyrrolidone and other optional ingredients known in the art to permit tableting the mixture by known methods. The tablets may, if desired, be coated using known methods and excipients which may include enteric coating using for example hydroxypropylmethylcellulose phthalate. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by known methods and, if desired, provided with enteric coatings in a known manner. The contents of the capsule may be formulated using known methods so as to give sustained release of the active compound. The tablets and capsules may conveniently each contain 1 to 50 mg of the active compound.

Other dosage forms for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxy-methylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil. The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example, water) before ingestion. The granules may contain disintegrants, eg an effervescent couple formed from an acid and a carbonate or bicarbonate salt to facilitate dispersion in the liquid medium.

The therapeutically active compounds of formula I may be formulated into a composition which the patient retains in his mouth so that the active compound is administered through the mucosa of the mouth.

5

Dosage forms suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

10 Dosage forms suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

15 Dosage forms for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as a mineral oil, petrolatum and/or a wax, e.g. paraffin wax or beeswax, together with a potential
20 transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream, gel or ointment base. The amount of active compound contained in a topical formulation should be such that a therapeutically effective amount of the compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

25

The therapeutically active compound of formula I may be formulated into a composition which is dispersed as an aerosol into the patients oral or nasal cavity. Such aerosols may be administered from a pump pack or from a pressurised pack containing a volatile propellant.

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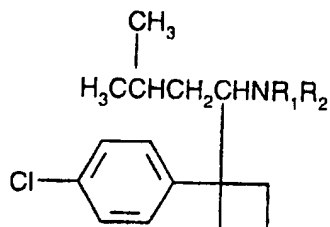
The therapeutically active compounds of formula I used in the method of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs
35 containing the compound to be infused which is continuously released for example by osmosis and implants which may be (a) liquid such as an oily suspension of the

compound to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or a lipophilic ester or (b) solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing part of the compound to be delivered. The amount of active compound present in an internal source should be such that a therapeutically effective amount of the compound is delivered over a long period of time.

10 In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

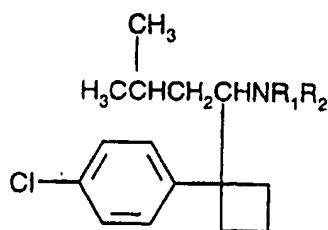
15 In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

The invention further provides the use of a compound of formula I



20 including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl, in the manufacture of a medicament for the treatment and/or prophylaxis of hyperlipidaemia, hypercholesterolaemia or hypertriglyceridaemia

25 In another aspect, the invention provides a pharmaceutical composition for the treatment and/or prophylaxis of hyperlipidaemia, hypercholesterolaemia or hypertriglyceridaemia, comprising a compound of formula I



including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl, in conjunction with a pharmaceutically acceptable diluent or carrier.

5 The present invention further provides a method of lowering lipid levels in the human body comprising the administration of a compound of formula I in conjunction with a pharmaceutically acceptable diluent or carrier to a human in need thereof. Preferably the lipid is a cholesterol or a triglyceride.

10 The present invention further provides a method of increasing the HDL cholesterol to LDL cholesterol ratio in the human body, comprising the administration of a compound of formula I in conjunction with a pharmaceutically acceptable diluent or carrier to a human in need thereof.

15 The present invention further provides the use of a compound of formula I in the manufacture of a medicament for lowering lipid levels in the human body. Preferably the lipid is a cholesterol or a triglyceride.

20 The present invention further provides the use of a compound of formula I in the manufacture of a medicament for the prophylaxis of atherosclerosis, coronary heart disease and/or coronary artery disease in humans at increased risk of developing these conditions.

25 The present invention further provides the use of a compound of formula I in the manufacture of a medicament for increasing the HDL cholesterol to LDL cholesterol ratio in the human body.

30 The present invention further provides a pharmaceutical composition for lowering lipid levels in the human body comprising a therapeutically effective amount of a compound of formula I in conjunction with a pharmaceutically acceptable diluent or carrier. Preferably the lipid is a cholesterol or a triglyceride.

35 The present invention further provides a pharmaceutical composition for the prophylaxis of atherosclerosis, coronary heart disease and/or coronary artery disease in humans at increased risk of developing these conditions, comprising a

therapeutically effective amount of a compound of formula I in conjunction with a pharmaceutically acceptable diluent or carrier.

5 The present invention further provides a pharmaceutical composition for increasing the HDL cholesterol to LDL cholesterol ratio in the human body comprising a therapeutically effective amount of a compound of formula I in conjunction with a pharmaceutically acceptable diluent or carrier.

10 Compounds of formula I also have utility in the treatment of conditions associated with elevated Very Low Density Lipoprotein (VLDL), Intermediate Density Lipoprotein (IDL) or LDL levels, such as eruptive xanthomata, tuberous xanthomata, tendinous xanthomata and corneal arcus.

15 The efficacy of compounds of formula I in lowering lipid levels and increasing the HDL : LDL cholesterol ratio is illustrated by the following clinical trials. It will be appreciated by those skilled in the art that a 10 mg dose or 15 mg dose of sibutramine in the form of hydrochloride monohydrate is equivalent to 8.37 mg or 12.55 mg of sibutramine as free base respectively.

20 Trial 1

In a clinically supervised trial, 485 mild to moderately obese patients were randomised to receive placebo, sibutramine hydrochloride monohydrate (10 mg) or sibutramine hydrochloride monohydrate (15 mg) orally once daily for 12 months.
25 Statistically significant reductions in triglyceride levels were observed in both sibutramine groups compared to placebo at month 6.

	Percentage Change From Baseline		
Assessment Time	Placebo	Sibutramine(10 mg)	Sibutramine (15 mg)
Month 6	-3	-18*	-19**

* p< 0.05, ** p< 0.01 compared to placebo.

30 'Sibutramine' means sibutramine hydrochloride monohydrate

Trial 2

In a further clinically supervised trial, 160 obese patients following a very low calorie diet were randomised to receive placebo or sibutramine hydrochloride monohydrate (10 mg) once daily for 12 months. Statistically significant ($p < 0.05$) changes for a number of lipid variables were observed in favour of the sibutramine group, as illustrated in the following table:

Variable	Assessment time	Median as a percentage of normal range		p
		Sibutramine(10 mg)	Placebo	
Apolipoprotein B/A1 ratio	Month 6	-23%	-13%	0.03
	Month 12	-10%	-3%	0.02
Apolipoprotein B	Month 6	7%	15%	0.049
Triglycerides	Month 1	0%	6%	0.0014
	Month 6	-4%	4%	0.02
	Endpoint	0%	4%	0.04
VLDL triglycerides	Month 1	-4%	3%	0.045
	Month 6	-6%	3%	0.04
HDL+LDL triglycerides	Month 6	-4%	6%	0.0105
	Month 12	2%	13%	0.003
	Endpoint	1%	9%	0.008
LDL-cholesterol	Month 6	20%	32%	0.02
HDL-cholesterol	Month 12	34%	18%	0.003
	Endpoint	28%	18%	0.03
Total cholesterol/HDL cholesterol ratio	Month 12	-10%	-1%	0.02
LDL/HDL cholesterol ratio	Month 12	-10%	0%	0.0099
	Endpoint	-8%	0%	0.04

10

'Sibutramine' means sibutramine hydrochloride monohydrate

In obese patients with normal cholesterol levels sibutramine tended to reduce LDL cholesterol levels and increase HDL cholesterol levels. Significant increases in the ratios of HDL cholesterol to total cholesterol and HDL to LDL cholesterol were observed.

15

Further analysis of data

- 5 A meta-analysis of lipid profile based on weight lost, and a regression analysis comparing weight lost with changes in the co-morbid variable, was carried out on data from six clinical studies in obese patients in which fasting samples had been taken:

Summary of double-blind, placebo-controlled sibutramine hydrochloride monohydrate studies with fasting data

10

Study	Co-morbid condition	Duration (weeks)	No. of patients included in meta-analysis			
			Placebo	10 mg	15 mg	1-30 mg
1		24	102	116	114	694
2		52	78	81	-	81
3	Metabolic syndrome	12	76	74	-	74
4	Dyslipidaemia	16	90	87	-	87
5	Diabetes	12	41	-	45	45
6	Pre-diabetes	24	58	-	50	50
Total no. of patients ^a :			445	358	209	1031

^a Corresponding numbers of patients may be less for a given variable due to missing values.

- 15 Each meta-analysis was performed parametrically on the percentage change for lipids from baseline to endpoint (LOCF).

20 Data for all sibutramine hydrochloride monohydrate doses (1-30 mg) combined, sibutramine hydrochloride monohydrate 10 mg and 15 mg compared with placebo, categorised by all patients and those losing $\geq 5\%$ and $\geq 10\%$, is presented. The changes in risk for the sibutramine hydrochloride monohydrate patients who lost weight, ie with pharmacological intervention, were tested against the all patient placebo group, ie non-pharmacological intervention, using the same meta-analysis techniques.

Summary of mean percentage change from baseline to endpoint for lipid variables in the meta-analysis of six studies with fasting lipids (LOFC analysis)

Wt loss category	Mean wt change ^a (kg)	Triglycerides	Cholesterol		
			Total	LDL	HDL
Placebo	-2.1	+2.4 (445)	+2.8 (445)	+5.0 (439)	+4.0 (443)
≥5% wt loss	-8.5	-12.4 (98)	-1.6 (98)	-2.4 (98)	+4.8 (98)
≥10% wt loss	-12.1	-14.4 (32)	-0.9 (32)	-5.6 (32)	+4.6 (32)
Sib 1-30 mg	-5.5	-6.7*** (1030)	+0.6** (1031)	+1.1** (1017)	+8.6*** (1028)
≥5% wt loss	-9.7	-15.8*** (524)	-2.1*** (524)	-1.4** (522)	+8.2** (524)
≥10% wt loss	-13.2	-20.5*** (234)	-4.5*** (234)	-5.0*** (234)	+9.8*** (234)
Sib 10 mg	-5.5	-8.0 (357)	+2.3 (358)	+3.2* (351)	+10.2** (356)
≥5% wt loss	-9.5	-16.2** (187)	0.4** (187)	+2.0 (186)	+10.1* (187)
≥10% wt loss	-13.4	-13.5** (76)	-0.9* (76)	0.9 (76)	+11.4 (76)
Sib 15 mg	-5.7	-8.2 (209)	-3.1** (209)	-2.4 (204)	+5.6** (207)
≥5% wt loss	-9.5	-14.0** (109)	-5.5* (109)	-4.4 (108)	+4.7 (108)
≥10% wt loss	-12.7	-22.2** (48)	-8.4** (48)	-7.5* (48)	+5.8 (48)

5 'Sib' means sibutramine hydrochloride monohydrate

a: Based on patients with triglyceride (TG) and total cholesterol (CHOL) data

Baseline values:

Placebo (mmol/l): TG 1.7; CHOL 5.6; LDL 3.5; HDL 1.3

Sib 1-30 mg (mmol/l): TG 1.8; CHOL 5.6; LDL 3.6; HDL 1.3

10 Sib 10 mg (mmol/l): TG 1.7; CHOL 5.6; LDL 3.4; HDL 1.3

Sib 15 mg (mmol/l): TG 1.9; CHOL 5.7; LDL 3.8; HDL 1.2

* p<0.05 vs. all placebo

** p<0.01 vs all placebo

*** p<0.001 vs. all placebo

() Number of patients.

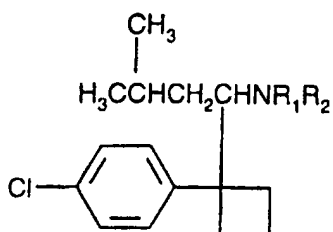
15 In this meta-analysis, patients treated with sibutramine hydrochloride monohydrate demonstrated statistically significant and clinically beneficial effects for all variables compared to placebo. More substantial positive effects are evident in those patients who lost clinically significant amounts of weight ie ≥5% and ≥10% of their baseline body weight.

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The above results support the utility of compounds of formula I in lowering lipid levels and increasing the HDL : LDL cholesterol ratio in the human body.

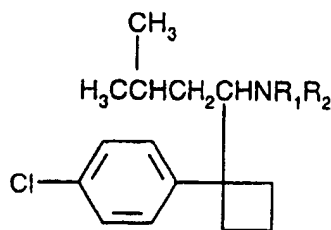
Claims

1. A method for the prophylaxis and/or treatment of hyperlipidaemia, hypercholesterolaemia or hypertriglyceridaemia, comprising the administration, to a human in need thereof, of a therapeutically effective amount of a compound of formula I



including enantiomers and pharmaceutically acceptable salts thereof in which R_1 and R_2 are independently H or methyl, in conjunction with a pharmaceutically acceptable diluent or carrier.

2. A method as claimed in claim 1 wherein the compound of formula I is *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride.
3. A method as claimed in claim 1 wherein the compound of formula I is *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride in the form of its monohydrate.
4. The use of a compound of formula I

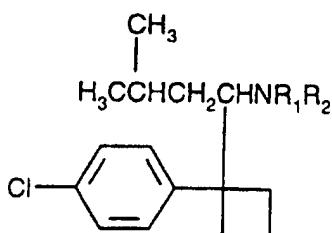


including enantiomers and pharmaceutically acceptable salts thereof in which R_1 and R_2 are independently H or methyl, in the manufacture of a medicament for the prophylaxis and/or treatment of hyperlipidaemia, hypercholesterolaemia or hypertriglyceridaemia.

5. The use as claimed in claim 4 in which the compound of formula I is *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride.

6. The use as claimed in claim 4 in which the compound of formula I is *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate.

5 7. A pharmaceutical composition for the prophylaxis and/or treatment of hyperlipidaemia, hypercholesterolaemia or hypertriglyceridaemia comprising a therapeutically effective amount of a compound of formula I



10 including enantiomers and pharmaceutically acceptable salts thereof in which R₁ and R₂ are independently H or methyl, in conjunction with a pharmaceutically acceptable diluent or carrier.

8. A pharmaceutical composition as claimed in claim 7 in which the compound of
15 formula I is *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride.

9. A pharmaceutical composition as claimed in claim 7 in which the compound of
20 formula I is *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate.

10. A method of lowering lipid levels in the human body comprising the
administration of a compound of formula I, as defined in claim 1, to a human in need
thereof in conjunction with a pharmaceutically acceptable diluent or carrier.

25

11. The use of a compound of formula I, as defined in claim 4, in the manufacture
of a medicament for lowering lipid levels in the human body.

12. The use of a compound of formula I, as defined in claim 4, in the manufacture
30 of a medicament for the prophylaxis of atherosclerosis, coronary heart disease and/or
coronary artery disease in humans at increased risk of developing these conditions.

13. A method of prophylaxis of atherosclerosis, coronary heart disease and/or coronary artery disease in humans at increased risk of developing these conditions, comprising the administration of a compound of formula I, as defined in claim 1, in conjunction with a pharmaceutically acceptable diluent or carrier to a human in need thereof.

14. A method of increasing the high density lipoprotein cholesterol to low density lipoprotein cholesterol ratio in the human body, comprising the administration of a compound of formula I, as defined in claim 1, in conjunction with a pharmaceutically acceptable diluent or carrier to a human in need thereof.

15. The use of a compound of formula I, as defined in claim 4, in the manufacture of a medicament for increasing the high density lipoprotein cholesterol to low density lipoprotein cholesterol ratio in the human body.

15

16. A pharmaceutical composition for lowering lipid levels in the human body comprising a therapeutically effective amount of a compound of formula I, as defined in claim 7, in conjunction with a pharmaceutically acceptable diluent or carrier.

17. A pharmaceutical composition for the prophylaxis of atherosclerosis, coronary heart disease and/or coronary artery disease in humans at increased risk of developing these conditions, comprising a therapeutically effective amount of a compound of formula I, as defined in claim 7, in conjunction with a pharmaceutically acceptable diluent or carrier.

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18. A pharmaceutical composition for increasing the high density lipoprotein cholesterol to low density lipoprotein cholesterol ratio in the human body, comprising a therapeutically effective amount of a compound of formula I, as defined in claim 7, in conjunction with a pharmaceutically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/05040

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
P, X	M.E.J. LEAN: "Sibutramine - a review of clinical efficacy." INT. J. OBES.. vol. 21, no. SUPPLEMENT 1, 1997, pages s30-s36, XP002054667 see the whole document ---	1, 2, 4, 7, 10-18
P, X	M. WEISER ET AL.: "the pharmacologic approach to the treatment of obesity" J. CLIN. PHARMACOL.. vol. 37, no. 6, 1997, pages 453-473, XP002055054 see the whole document ---	1, 2, 4, 7, 10-18
X	GB 2 098 602 A (BOOTS CO.) 24 November 1982 cited in the application see the whole document -----	7, 8

☐ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex.

Special categories of cited documents

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- "&" document member of the same patent family

Date of the actual completion of the international search

9 February 1998

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Klaver, T

INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/EP 97/05040

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